Cellular Noise and The Aging Process

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Cellular aging is an irreversible process that is poorly understood. The process of aging however, has been correlated with other processes including the shortening of telomeres. While telomere shortening has dominated the current literature on aging, we are motivated by the recent work of Bennett-Baker *et al.*, in which another such correlation was discovered. This correlation is between age and the reactivation of genes on the inactive X-chromosomes in female mice. We propose two mathematical models to investigate the progression of aging at the cellular level. In the first model, we study the dynamics of aging using a discrete time dynamical system based on the competition between "noisy" and "noise-free" cells. Our preliminary results suggest the existence of three different qualitative outcomes. These outcomes are best described by exclusion and coexistence, where coexistence occurs under two dynamically distinct scenarios. In the second model, we consider a stage-structured model that incorporates stage dependent vital rates. Varying these rates is important as the accumulation of cellular error (noise) accelerates the aging process.

Aging has been a topic of great interest to scientists. A definition of aging is rarely agreed upon among researchers but it includes all time-dependent processes that occur within an organism whether adverse or not. Among biologists, aging is more narrowly referred to as the gradual and irreversible decrease in function of a system of cells with time. Over the years, many theories on aging have been developed and tested in an effort to understand this process. Some of these theories include the predetermined life span theory [1], telomere shortening theory [6], and the cross linking theory [7]. The predetermined life span theory states that an organism has a fixed amount of time to live which is predetermined in the embryonic cell. More precisely, the organism's natural life span is based on the number of divisions that cells undergo during a lifetime [1]. The telomere shortening theory suggests that the shortening of telomeres, which occurs with each mitotic division (in the absence of telomerase), may be responsible for aging. This gradual change in length of the telomeric DNA causes changes in the proteins around the telomere, which can lead to a change in the gene expression of the entire chromosome [4]. In addition, shortened telomeres may cause the misalignment of the chromosomes during meta-phase. As a result, some scientists now view telomeres as cellular timers that trigger cells to cease function when time (length) runs out [5]. Lastly, the cross linking theory states that aging is caused by the presence of large, linked molecules. These large molecules are hypothesized to accumulate in the cell and cause cellular and tissue damage in numerous ways including decreasing tissue elasticity and impeding intra- and inter-cellular transport [3].

In the first model we apply a modified discrete time Leslie-Gower framework to study the competitive dynamics of a system in which the population is denoted by error-free (P) and error cells

(Q). We study the model analytically by establishing conditions for stability of the equilibria. The trivial equilibrium, E_0, corresponds to the extinction of both P and Q and it is stable when both of these classes do not reproduce fast enough to replace themselves. The boundary equilibrium, E_1, represents the exclusion of P cells. There does not exist a corresponding boundary equilibrium for the exclusion of Q cells. Most importantly is the existence of positive equilibria. For our model, we have shown that there may be up two positive equilibria (E_2, E_3). We have shown that the existence condition for two positive equilibria implies the stability of the boundary equilibrium. In this case, one of the positive equilibrium points acts as a saddle while the other is locally stable (along with the boundary equilibrium). When only a single positive equilibrium point exists, we have shown that the boundary equilibrium is unstable and numerical results suggest that the positive equilibrium is globally stable. In addition, we have found the existence of a saddle node bifurcation characterized by the two positive equilibria colliding and annihilating one another. One other result of particular interest is that coexistence can be achieved when the inter-specific competition is greater than the intra-specific competition (a result that is inconsistent with Lotka-Volterra competition models).

A stage structured model was introduced as an alternative to the discrete time competition model. The continuous variable, mean expression ratio, χ_i/χ_a was partitioned into four distinct classes where χ_i and χ_a represent genes on the inactive and active χ chromosomes of the female mice respectively. This classification, while arbitrary, is important as it allows the various stages to possess different vital rates. The four stages for this model are given by: (1) Stage 0 cells where $\chi_i/\chi_a = 0$ (stem cells), (2) Stage 1 cells where $\chi_i/\chi_a < 0.5\%$, (3) Stage 2 cells where $0.5\% < \chi_i/\chi_a < 2\%$, and (4) stage 3 cells where $\chi_i/\chi_a > 2\%$. To run a numerical simulation of this model, functions, g_i, were chosen to dictate when (i.e. at what time step) differentiated cells in class i would transition. The choice of g_i is arbitrary with the only constraint being that it be monotonically decreasing.

These results are relatively consistent with the data obtained in the experiments of Bennett-Baker *et al.* in the sense that it takes many generations for cells with comparatively high amounts of error to accumulate. Since the functions g_i can be

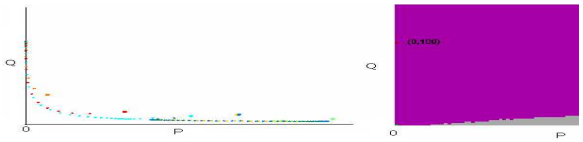
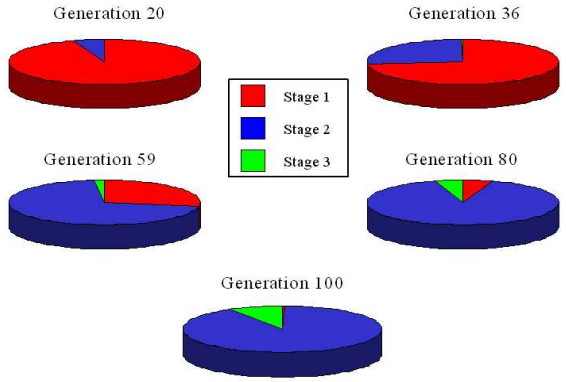


Figure 1a illustrates the influence of the nearby saddle node which acts as a separatrix for the basins of attraction of the multiple attractors (bistability). Figure 1b depicts the basins of attraction for multiple attractors (boundary and interior equilibria).



Simulation for 100 generations show that 90% of the population are in classes 2 and 3 respectively while 1% remain in classes 0 and 1.

any monotonically decreasing functions, it may be possible to better fit the data as these functions are altered. The simulations did provide an informative view of the frequency of cells within each stage throughout time (as conducted in the experiment). These results match the findings of the experiments of [2] qualitatively; the expression of inactivate genes stays extremely low for an extended period of time, and then begins to increase at an increasing rate. Of course this exemplifies the particular choice of the nonlinear transition functions, g_i.

Acknowledgements

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